MSAC Application 1767

Immunohistochemistry testing for Claudin 18 expression in patients with gastric or gastro-oesophageal junction cancers, to determine eligibility for PBS subsidised zolbetuximab treatment

PICO Set Document

Population

Describe the population in which the proposed health technology is intended to be used:
Immunohistochemistry (IHC) testing for Claudin (CLDN18.2) expression to determine PBS eligibility for zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 negative (HER2-) gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumours are CLDN18.2 positive.

Zolbetuximab, a monoclonal antibody targeting claudin-18 isoform 2 (CLDN18.2), is proposed to be funded for patients with CLDN18.2-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GOJC) adenocarcinoma.

CLDN18.2 status in G/GEJC is determined by the percentage of tumor cells (% TC) showing moderate-to-strong membranous CLDN18 staining above background. The CLDN18 threshold for a positive result is ≥75% TCs showing moderate-to-strong membranous staining above background, while <75% TCs showing moderate-to-strong membranous staining is indicative of a negative result.

Patients are selected with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive (defined as ≥75% of tumour cells demonstrating moderate to strong membranous CLDN18 immunohistochemical staining) as determined by a validated test.

Gastric or gastroesophageal junction (GEJ) cancer comprises cancer that arises from the epithelial lining of the stomach and the gastroesophageal junction (GOJ) (between the stomach and the oesophagus), respectively[i]. Tumours in the GOJ may be classified as either gastroesophageal junction cancer (GOJC) or oesophageal cancer depending on how far from the GOJ they arise. Given the interrelatedness of GC and GOJC, the paucity of data from GOJC as a discrete disease entity, and the fact that patients with GC and GOJC have been the combined target population in clinical trials, data from GC are applied to the G/GOJC population in this dossier when data from GOJC are not available[ii].

G/GOJC is an important cancer globally, responsible for over one million new cases in 2020 and an estimated 769,000 deaths (equating to one in every 13 deaths globally), ranking 5th for incidence and 4th for mortality[iii]. G/GOJC rates are 2-fold higher in men than in women and it is the most commonly diagnosed cancer and the leading cause of cancer death in several South-Central Asian countries. Highest incidence rates are found in Japan and Mongolia, and Eastern Europe, especially compared with North America, Northern Europe, and Africa where rates are relatively low. Early stage G/GOJC is often asymptomatic, and common symptoms in later stage disease are often non-specific; these may include dysphagia, asthenia, indigestion, vomiting, stomach pain, bloating, weight loss, early satiety and/or iron deficiency anaemia.[10] The lack of specific or pathognomonic symptoms prevents early diagnosis in the absence of screening programs and it is estimated that 80%–90% of patients in Western countries will present with locally advanced or metastatic tumours that are minimally resectable.[11]

The prognosis for patients with G/GOJC remains poor despite some improvement in survival between 1980 and 2010 following the introduction of a multidisciplinary management approach

and the use of palliative chemotherapyiv. Gastric cancers (including GOJC) have a disproportionate impact on Australians with lower socioeconomic backgrounds, who were 1.4 and 1.5 times more likely to die from GC and OAC respectively in 2012-2016 than the highest socioeconomic group, with even lower survival for Indigenous Australians[1] (AIHW, 2018)

An Australian study by Kumarasinghe et al., 2017 estimated the proportion of G/GOJC patients who are HER2 negative as 86.1%. The proportion of patients ≥ 75% CLDN18.2 expression is estimated 38% from SPOTLIGHT and GLOW.

The PBAC has noted that the clinical need for effective treatments in this therapeutic area is high (Nivolumab PSD Nov 2021, para 7.1, given the poor prognosis for patients and the poor efficacy and high toxicity of current treatments.

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

Early stage G/GEJC is often asymptomatic, and common symptoms in later stage disease are often non-specific. It is estimated that 80%–90% of patients in Western countries will present with locally advanced or metastatic tumors that are minimally resectable due to the lack of disease-specific symptoms and screening programs.

The non-specific symptoms of G/GEJC results in some patients waiting up to one year before seeking medical attention. Furthermore, healthcare practitioners (HCP) rarely consider a GC diagnosis immediately because symptoms are vague, resulting in delayed referral to specialists. This results in delayed diagnosis, leading to a high proportion of patients initially diagnosed with locally advanced unresectable/metastatic disease, which has a poor prognosis. HCPs feel defeated when discussing treatment options with HER2 negative patients who have advanced/metastatic disease due to the lack of targeted therapies.

Diagnosis of G/GEJC is based on biopsies taken during endoscopy, endoscopic mucosal resection (EnMR), endoscopic submucosal dissection (ESD) or gastrectomy. Treatment considerations in G/GEJC are determined by stage and extent of disease, and if the cancer can be completely removed by surgery (i.e., is resectable). The American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system is used to stage GC and GEJC (which is staged like adenocarcinoma of the esophagus and does not include stage grouping). An AJCC stage is assigned based on the growth and characteristics of the primary tumor (T), the extent of spread to nearby lymph nodes (N), and the presence or absence of distant metastasis (M).

Patients with locally advanced unresectable/metastatic cancer are further classified according to HER2 status.

These are patients with gastric cancer that are going to an endoscopy for diagnosis and sample to test for biomarkers (HER2, PDL1 and our CLDN18.2).

[1] AIHW 2018 - https://www.aihw.gov.au/reports/cancer/cancer-in-indigenous-australians/contents/cancer-type/oesophageal-cancer-c15

Provide a rationale for the specifics of the eligible population:
A significant unmet need exists in G/GEJC, especially in advanced stages. G/GEJC is difficult to detect and is typically diagnosed in later stages. It is curable if diagnosed at an early stage, but survival is very low in later stages.

The prognosis for patients with advanced G/GEJC remains poor despite some improvement in survival between 1980 and 2010 following the introduction of a multidisciplinary management approach and the use of palliative chemotherapy.

The availability of HER2-targeted treatments further improved survival of patients with HER2-positive G/GEJC (approximately 15%-22% of cases, although this figure varies across the literature).

In the US, the 5-year survival rate for G/GEJC was estimated at 35.7%.

G/GEJC is frequently diagnosed at an advanced stage, with metastatic GC accounting for one-third of all initially diagnosed GC cases, negatively impacting survival outcomes. Countries with national GC screening programs (vs. those without) have a lower proportion of patients diagnosed with advanced disease.

Are there any prerequisite tests?
Yes

The patient's human epidermal growth factor receptor 2 status (HER2 status, ie negative) requires to be known.

Are the prerequisite tests MBS funded?
Yes

HER2 testing is done as part of the standard work up for G/GEJ cancer diagnosis and staging. A tumour is defined as being HER2- if a lack of HER2 expression is confirmed by an IHC score of 0, 1+, or IHC 2+ with additional confirmation as negative by in-situ hybridization (ISH) testing.

The relevant tests on the Medical Benefits Schedule (MBS) for determining HER2 status are:

MBS Item 72848: *Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 of the following antibodies - oestrogen, progesterone and c-erb-B2 (HER2).*
https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=72848&qt=item&criteria=HER2

Fee: $74.50 Benefit: 75% = $55.90 85% = $63.35

MSAC Item 73342: *An in situ hybridisation (ISH) test of tumour tissue from a patient with metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, with documented evidence of human epidermal growth factor receptor 2 (HER2) overexpression by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+ on the same tumour tissue sample, requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to HER2 gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme are fulfilled.*
https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73342&qt=item

Fee: $315.40 Benefit: 75% = $236.55 85% = $268.10

Please provide details to fund the prerequisite tests:
HER2 testing is done as part of the standard work up for G/GEJ cancer diagnosis and staging. A tumour is defined as being HER2- if a lack of HER2 expression is confirmed by an IHC score of 0, 1+, or IHC 2+ with additional confirmation as negative by in-situ hybridization (ISH) testing.

MBS Item no. 72848

Group P5 - Tissue Pathology

Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 of the following antibodies - oestrogen, progesterone and c-erb-B2 (HER2)

MSAC Item 73342:

Group P7 - Genetics

An in situ hybridisation (ISH) test of tumour tissue from a patient with metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, with documented evidence of human epidermal growth factor receptor 2 (*HER2*) overexpression by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+ on the same tumour tissue sample, requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to *HER2* gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme are fulfilled.

Fee: $315.40 Benefit: 75% = $236.55 85% = $268.10

MSAC Item 73061 is less used

MSAC Item 73061

Group P6 - Cytology

Immunocytochemical examination of material obtained by procedures described in items 73045, 73047, 73049, 73051, 73062, 73063, 73066 and 73067 for the characterisation of a malignancy by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 of the following antibodies - oestrogen, progesterone and c-erb-B2 (HER2)

Intervention

Name of the proposed health technology:
Test: Ventana® CLDN18 (43-14A) RxDx Assay

Treatment: VYLOY (zolbetuximab) in combination with fluoropyrimidine- and platinum-containing chemotherapy

Describe the key components and clinical steps involved in delivering the proposed health technology:
The Ventana® CLDN18 (43-14A) RxDx Assay is diagnostic that will be used to assess CLDN18.2 status of gastric cancer patients (HER2 negative with unresectable locally advanced or metastatic G/GEJ adenocarcinoma) to help determine eligibility for treatment with PBS listed zolbetuximab.

The CLDN18.2 involves taking a biopsy of the cancer tumour and performing an immunohistochemical (IHC) assay to detect the percentage of CLDN18.2 expression (≥ 75%). The testing would be done by a pathologist alongside other immunohistochemical tests which are done routinely (i.e., PD-L1), and it is proposed that the test is a pathologist determinable test.

Provide details of how the proposed health technology is expected to be used, including frequency of use, mode of delivery, clinical setting, specialist training and provider type. Describe the required infrastructure for use of the technology, and whether the health system is currently able to provide this. State whether the proposed health technology is currently funded (in the public or private setting) in Australia for the same or another clinical indication.

The proposed health technology, Ventana® CLDN18 (43-14A) RxDx Assay, will be used once per patient, per lifetime. It is proposed that one CLDN18.2 test be performed once for each patient as part of the diagnostic biopsy, which is already part of standard management. There is no known role for CLDN18.2 testing in monitoring a patient's response to zolbetuximab treatment.

The proposed health technology is currently under review by the TGA and the infrastructure for the use of the technology is in development.

The proposed health technology is not currently funded in the public or private setting.

Identify how the proposed technology achieves the intended patient outcomes:

The CLDN18.2 protein has been widely studied given its central role in G/GEJC[v],[vi],[vii]. IHC is the standard method for detecting CLDN18.2 [viii]. Among G/GEJC biomarkers, CLDN18.2 is highly prevalent with quantitative expression studies reporting that approximately 70% of gastric adenocarcinomas express CLDN18.2 [ix]. Moreover, a recent study of 350 patients with G/GEJC reported that approximately 33% of the study population had high CLDN18.2 expression (2+ and 3+ intensity in ≥75% of tumour cells) [x].

CLDN18.2 is expressed in both diffuse-type tumors and intestinal-type tumours[viii]. Tumours with diffuse histology, more often seen in the US and other Western countries, are associated with a poorer prognosis than those with intestinal histology [xi]. In normal gastric epithelial tissue, claudins in tight junctions are inaccessible from either the apical or basal surface [ix],[xii],[xiii]. Outside of differentiated gastric mucosa cells of the pit and base regions of the gastric glands, CLDN18.2 is not detectable in any other normal cell types in the body [ix]. However, malignant transformation in gastric cancer disrupts the tight junction and normal cell polarity, as well as CLDN18.2 localization, resulting in aberrant cell surface exposure of CLDN18.2 epitopes. In G/GEJC tumour tissue, these CLDN18.2 epitopes exposed on the tumour cell surface provide a target for CLDN18.2-targeted mAbs.

The VENTANA CLDN18 (43-14A) RxDx Assay is a semi-quantitative IHC assay using mouse monoclonal anti-claudin 18, clone 43-14A, intended for laboratory use in the assessment of CLDN18 protein in formalin-fixed, paraffin-embedded (FFPE) gastric adenocarcinoma including GEJ tissue specimens by light microscopy. This assay is used with OptiView DAB IHC Detection Kit for staining on a BenchMark IHC/in situ hybridization (ISH) instrument. The intended use setting of the VENTANA CLDN18 (43-14A) RxDx Assay is indicated as an aid in identifying patients with gastric or GEJ adenocarcinoma who may be eligible for treatment with VYLOY® (zolbetuximab).

CLDN18.2 status in G/GEJC is determined by the percentage of tumor cells (% TC) showing moderate-to-strong membranous CLDN18 staining above background. The CLDN18 threshold

for a positive result is ≥75% TCs showing moderate-to-strong membranous staining above background, while <75% TCs showing moderate-to-strong membranous staining is indicative of a negative result.

The VENTANA CLDN18 (43-14A) RxDx Assay has demonstrated strong analytic validity and consistent performance across a series of analytical verification assessments.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
Yes

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
The proposed health technology, Ventana® CLDN18 (43-14A) RxDx Assay will be the only CLDN18 assay in Australia.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):
No

Provide details and explain:
N/A

Accessibility
In the management of metastatic G/GEJC, taking biopsy specimens is currently part of standard practice and diagnostic work-up. It is proposed that CLDN18.2 expression testing can be carried out on the tissue sample when a patient is found to have G/GEJC. As part of standard practice, patients with advanced disease would have had a biopsy taken as part of initial diagnosis and use of their archival sample could be acceptable for assessing CLDN18.2 expression.

As IHC staining is a common procedure, CLDN18.2 IHC testing can be carried out in any pathology laboratory holding the appropriate accreditation. As IHC testing does not require a large volume of tissue, tissue availability shouldn't limit access. CLDN18.20 expression testing can be carried out on archival tissue samples taken as part of standard diagnostic procedures.

Frequency
It is proposed that one CLDN18.2 test be performed once for each patient as part of the diagnostic biopsy, which is already part of standard management. There is no known role for CLDN18.2 testing in monitoring a patient's response to zolbetuximab treatment.

Sample consideration
There is no known role for CLDN18.2 testing in monitoring a patient's response to zolbetuximab treatment.

Testing considerations
IHC testing is a well-established technique in all major pathology labs. Laboratories already have the platform infrastructure to perform CLDN18.2 IHC testing. The reagents and relevant regents will be available upon listing of VENTANA CLDN18 (43-14A) RxDx Assay on the ARTG.

It is acknowledged that there are differences between CLDN18.2 antibody assays for immune cell staining. Consequently, it is important that the antibody / test being used to assess CLDN18.2

status is aligned to the drug being considered. In this instance, the VENTANA CLDN18 (43-14A) RxDx Assay and CLDN18.2 expression ≥ 75% cut point should be used to determine eligibility for zolbetuximab.

If applicable, advise which health professionals will be needed to provide the proposed health technology:
The application recommends that ordering CLDN18.2 testing be restricted to gastroenterologists and oncologists once a diagnosis of HER2 negative unresectable locally advanced or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma has been established.

A certified pathologist would be responsible for conducting the testing and reporting of results. It is proposed that CLDN18.2 testing be eligible to be carried out in any pathology laboratory holding the appropriate accreditation to claim pathology services through the MBS.

Delivery of the CLDN18.2 test results would be provided by a pathologist with knowledge and expertise in testing for gastric cancer and immunohistochemistry testing. IHC testing is a well-established technique in all major pathology laboratories. Laboratories already have the platform infrastructure. The CLDN18.2 antibody and reagents to perform CLDN18.2 IHC testing are the only additional resource required.

As a consequence, billing of the intervention would be done by the pathologist.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
It is not anticipated that any other professional, other than a certified pathologist would be able to conduct IHC testing for CLDN18.2 expression.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
The application recommends that ordering CLDN18.2 testing be restricted to gastroenterologists and oncologists once a diagnosis of HER2 negative unresectable locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction (GC/GOJ adenocarcinoma) has been established.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?
Yes

Provide details and explain:
A certified pathologist would be responsible for conducting the test and reporting the results. Consistent with introduction of diagnostic tests associated with access to other targeted therapies, pathologist training and quality assurance programs would be developed with respect to delivery of diagnostic tests for access to treatments targeting the CLDN18.2 pathway on the PBS. This would address interpretation of the test results for CLDN18.2 positivity specific to the Ventana® CLDN18 (43-14A) RxDx Assay.

CLDN18.2 testing will be available to private and public patients.

In addition, Astellas is planning to facilitate one-day peer-to-peer workshops for Australian pathologists, with a training effectiveness performed with those who participate. This results in pathologists having greater experience in performing the test and applying the scoring methods.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

☒ Consulting rooms
☒ Day surgery centre
☐ Emergency Department
☐ Inpatient private hospital
☐ Inpatient public hospital
☒ Laboratory
☒ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?
Yes

Please provide additional details on the proposed health technology to be rendered outside of Australia:
N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:
Test Comparator: "No testing", as testing for CLDN18.2 is not currently funded, nor available or part of treatment algorithm.

Treatment Comparator: Nivolumab in combination with chemotherapy, for example, FOLFOX (oxaliplatin + folinic acid + fluorouracil) or FOLFIRI (Folinic acid, fluorouracil and irinotecan). There is no recommendation for one specific chemotherapy. The choice of regimen depends on patient characteristics, previous treatment and clinician choice.

List any existing MBS item numbers that are relevant for the nominated comparators:

As the proposed comparator is no testing, there are no eligible MBS items.

Please provide a rationale for why this is a comparator:

Test Comparator: As testing for CLDN18.2 is not currently funded, the appropriate comparator is 'no testing'.

Treatment Comparator: The current management for treatment naive patients with locally advanced or metastatic GC/GOJC is nivolumab in combination with chemotherapy, FOLFOX or FOLFIRI as the currently listed treatment. Nivolumab was the first immunotherapy to be listed on the PBS for the treatment of patients; recommended by the PBAC in March 2022 and PBS listed 1 October 2022.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator? (please select your response)

☐ None – used with the comparator
☐ Displaced – comparator will likely be used following the proposed technology in some patients
☐ Partial – in some cases, the proposed technology will replace the use of the comparator, but not all
☒ Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:
The proposed medical service (CLDN18.2 testing) facilitates eligibility to treatment with zolbetuximab in combination with chemotherapy and is expected to treat all HER-2 negative, locally advanced or metastatic G/GEJC patients with CLDN18.2 expression ≥75%.

HER-2 negative, locally-advanced or metastatic G/GEJC patients with CLDN18.2 expression <75% can elect receive nivolumab in combination with chemotherapy.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator): (please select your response)

☒ Health benefits
☒ Health harms
☐ Resources
☐ Value of knowing

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:
Test-related: Efficacy and safety outcomes of zolbetuximab with and without prior CLDN18.2 testing; Re-biopsy rates

Test outcomes: Trial based (evidentiary standard) CLDN18.2 IHC assay analytical performance; Comparative performance of CLDN18.2 testing methods; Clinical utility (test plus drug combination).

Healthcare resources: Cost of testing per case; re-biopsy rates; test turn-around time; estimated number of patients being tested.

Proposed MBS items

How is the technology/service funded at present? (for example: research funding; State-based funding; self-funded by patients; no funding or payments):
There is no funding.

Proposed item details

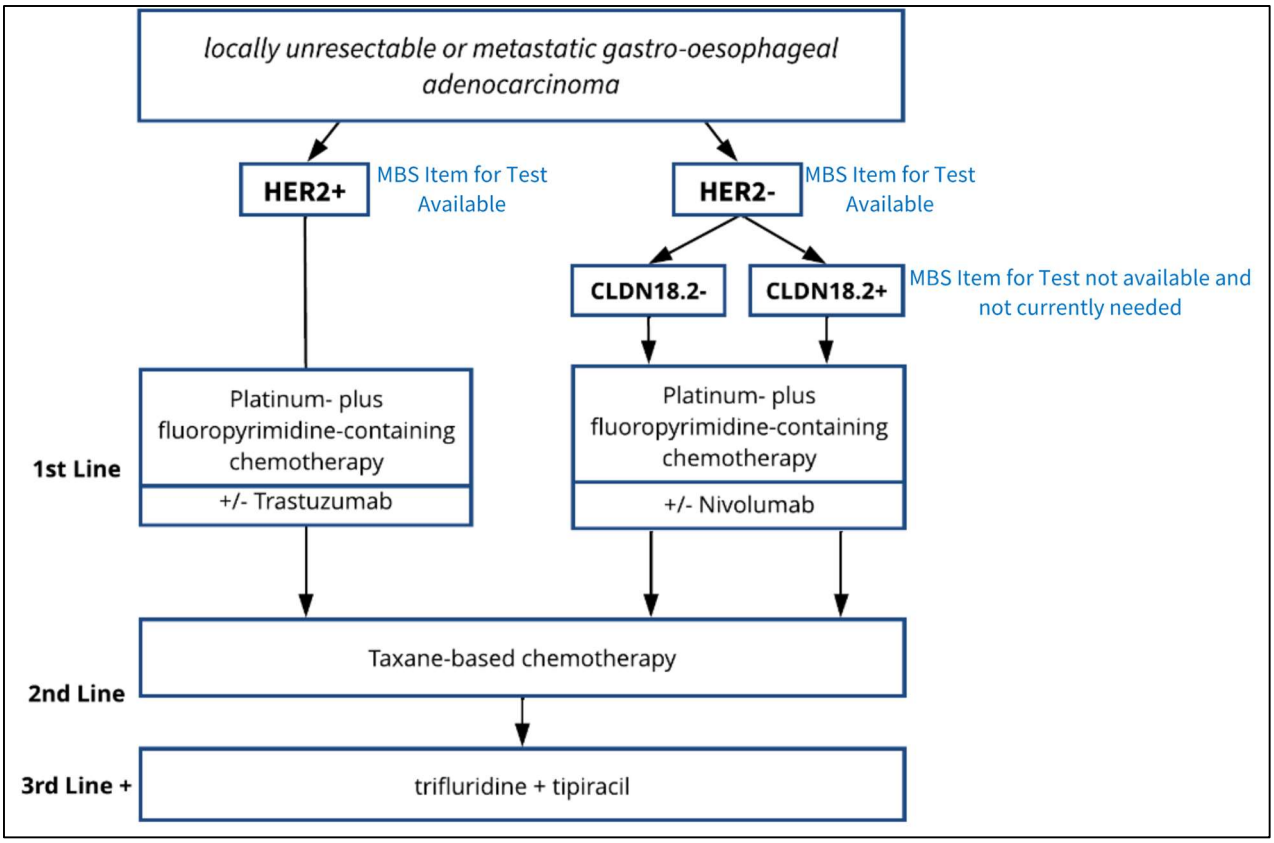
MBS item number (where used as a template for the proposed item)	AAAAA
Category number	Category 6
Category description	Pathology Services
Proposed item descriptor	Immunohistochemical examination of tumour tissue from a patient diagnosed with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 negative gastric or gastroesophageal junction adenocarcinoma to determine the requirements relating to CLDN18.2 expression (tumor cells ≥75%) for access to zolbetuximab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.
Proposed MBS fee	To be fully determined Fee: $550 Benefit: 75% = $412.50 85% = $467.50
Indicate the overall cost per patient of providing the proposed health technology	Includes MBS fee plus additional costs not captured within the PBS fee. To be determined (TBD)
Please specify any anticipated out of pocket expenses	Specify whether there is likely to be a 'gap' amount the patient is likely to have to pay above and beyond the MBS fee claimed by the service provider. No gap
Provide any further details and explain	n/a

Algorithms

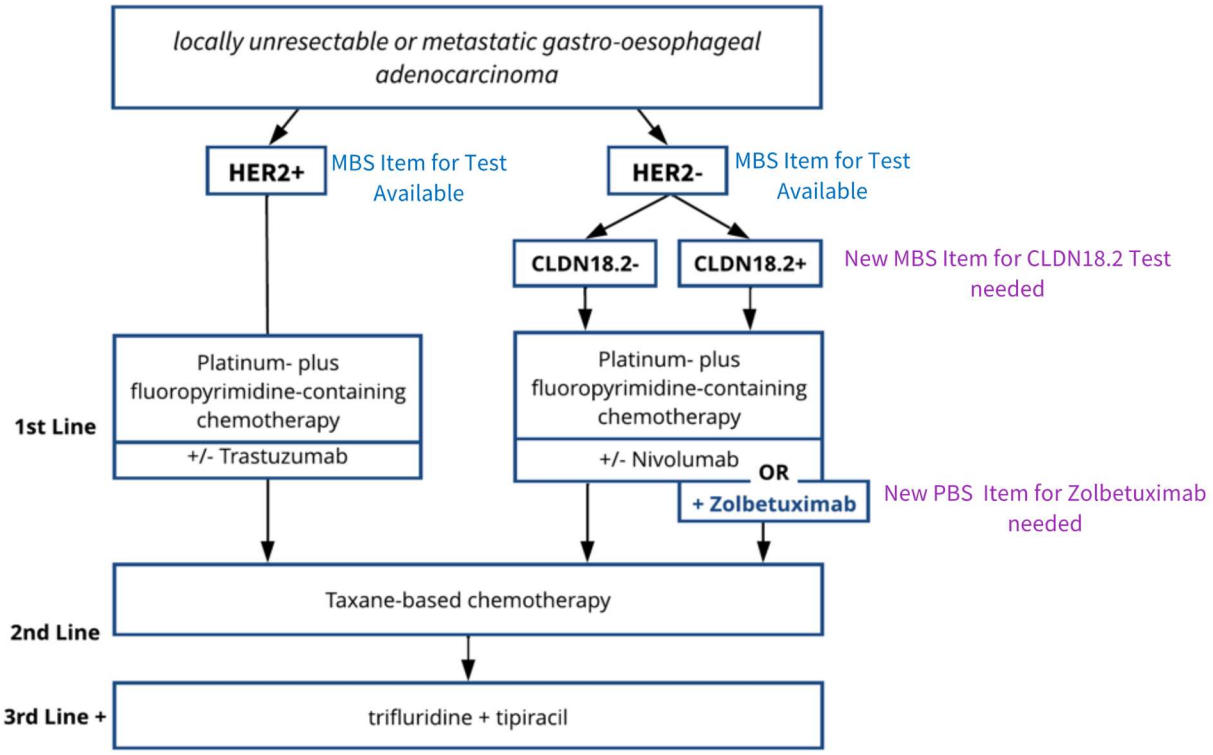
Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

Current Treatment Algorithm



Future Treatment Algorithm



The proposed positioning for zolbetuximab, based on the clinical trial evidence for HER2-negative & CLDN18.2-positive biomarker patients (new proposed MBS Item), as an addition to SOC first-line chemotherapy potentially, this may include patients who are otherwise contraindicated or ineligible for treatment with trastuzumab). Zolbetuximab could represent an alternative agent to nivolumab in this subset of patients.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?
Yes

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
Utilisation of the CLDN18.2 test to determine eligibility of treatment with PBS funded zolbetuximab.

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

Healthcare resources that are used in conjunction with CLDN18.2 IHC testing include tumour biopsy, which is already being conducted, not additional costs (MBS item number 30694, endoscopic ultrasound (endoscopy with ultrasound imaging), with or without biopsy, with fine needle aspiration for the diagnosis of pancreatic, biliary or gastric submucosal tumours).

30694

Group
T8 - Surgical Operations

Subgroup
1 - General

Endoscopic ultrasound (endoscopy with ultrasound imaging), with or without biopsy, with fine needle aspiration, for the diagnosis of 1 or more of pancreatic, biliary or gastric submucosal tumours, not in association with another item in this Subgroup (other than item 30484, 30485, 30491 or 30494) and other than a service associated with the routine monitoring of chronic pancreatitis.

Explain what other healthcare resources are used in conjunction with the comparator health technology:
Utilisation of PBS funded zolbetuximab.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:
Utilisation of PBS funded zolbetuximab.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:
The clinical management algorithms for previously untreated advanced gastric cancer indicated that the proposal is to add CLDN18.2 testing before chemotherapy is started, with patients shown to be HER2 negative offered zolbetuximab instead (and patients shown to be HER2 positive still being offered nivoluman in combination with chemotherapy instead).

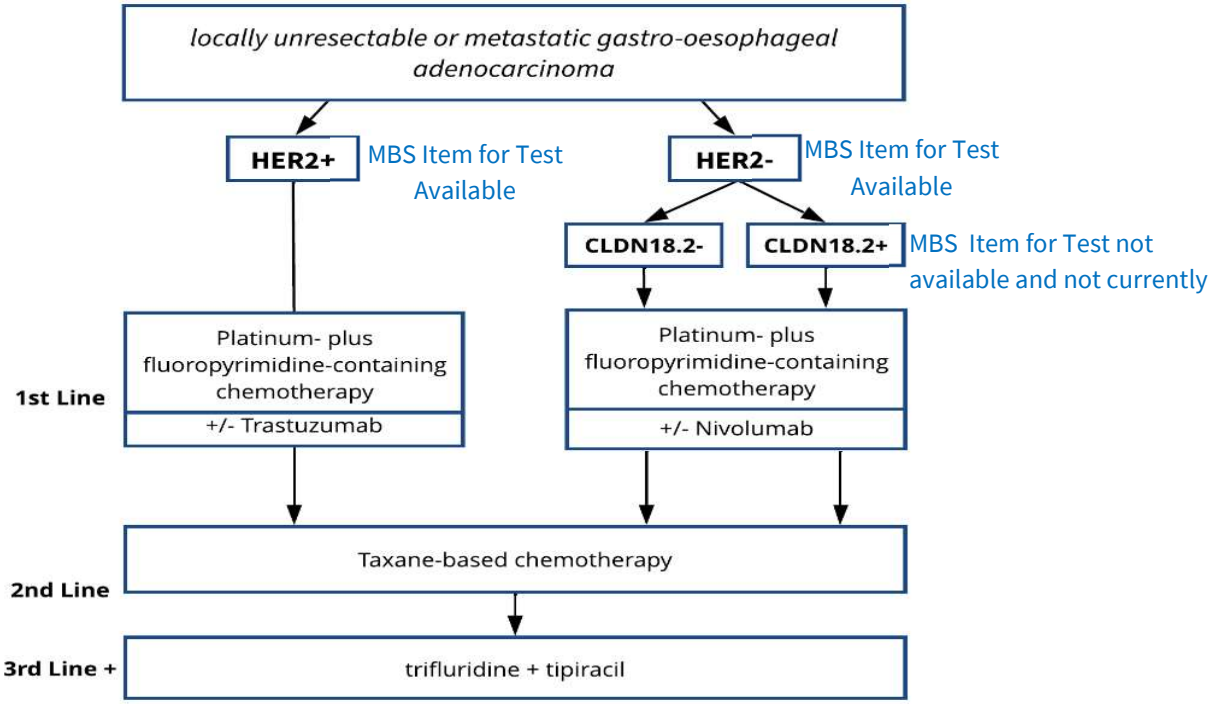
Zolbetuximab would be added to the currently available platinum-based chemotherapy regimens.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:
The clinical management algorithms for previously untreated advanced gastric cancer patients shown to be HER2 negative being offered platinum-based chemotherapy regimens.

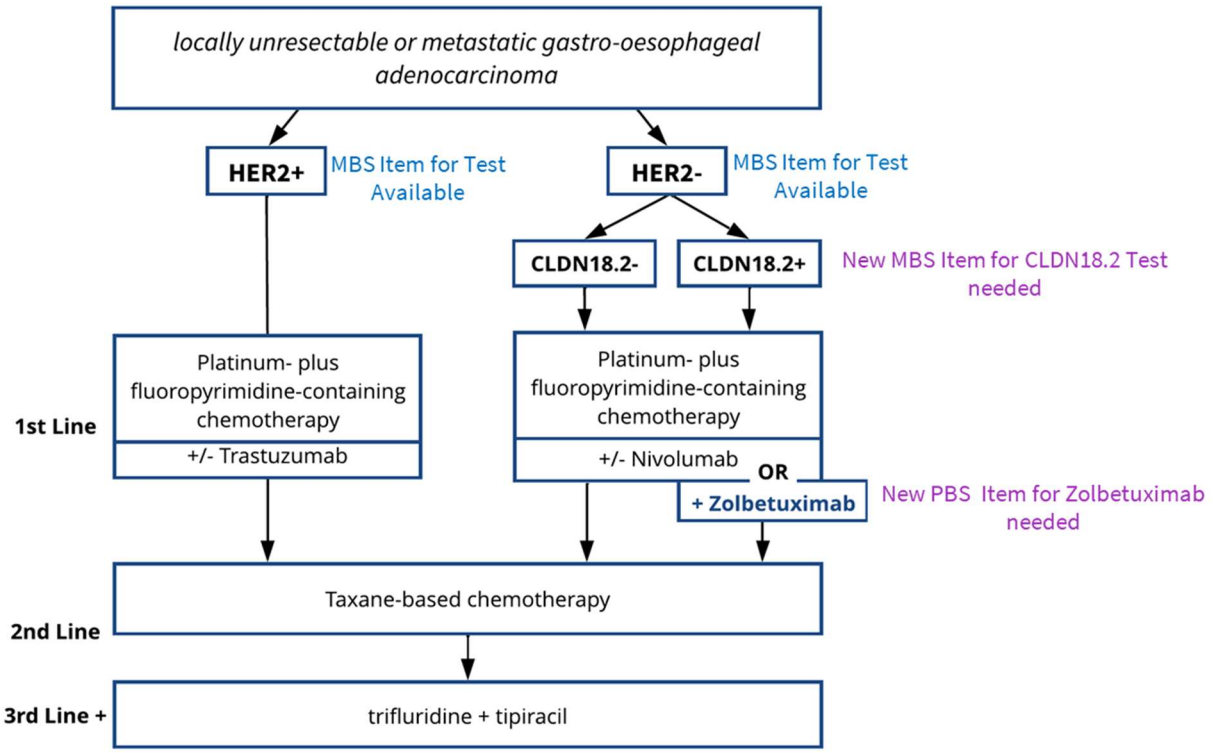
Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:
Utilisation of PBS funded zolbetuximab.

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Clinical management algorithm without the proposed health technology:



Clinical management algorithm with the proposed health technology :



Considering the clinical trial data for patients with HER2-negative and CLDN18.2-positive biomarkers, zolbetuximab is suggested to be integrated into the standard of care (SOC) first-line chemotherapy.

This positioning has the potential to encompass individuals who might be unsuitable or disqualified for trastuzumab treatment.

Notably, in this specific patient subgroup, zolbetuximab could emerge as a viable substitute to nivolumab.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☐ Superior
☒ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:
The clinical claim of active (ie test: Ventana® CLDN18 (43-14A) RxDx Assay plus treatment: VYLOY (zolbetuximab) is that it is non-inferior to comparator of test: no testing of CLDN18.2 plus nivolumab.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
Yes, in order to access PBS listing zolbetuximab.

Identify how the proposed technology achieves the intended patient outcomes:
Test, (Ventana® CLDN18 (43-14A) RxDx Assay) will allow access to PBS listed zolbetuximab, which will improve clinical outcomes for the patient.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management?	Yes
A change in health outcome?	Yes
Other benefits?	No

Please provide a rationale, and information on other benefits if relevant:
N/A

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:
Currently patients with G/GEJC cancer do not undergo CLDN18.2 testing, and thus, the funding of the test will be an additional cost to the MBS.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement', please do not attach full text articles; just provide a summary (repeat columns as required).

	Type of study design*	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1	Randomized 1:1, double-blinded, placebo-controlled, phase 3 trial	Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial.	SPOTLIGHT (NCT03504397) Patients (≥18 years) with CLDN18.2 expression in ≥75% tumour cells and HER2-negative. N= 283, zolbetuximab (800 mg/m^2 loading dose followed by 600 mg/m^2 Q3W plus mFOLFOX6 Q2W or N= 282, placebo Q3W plus mFOLFOX6 Q2W	https://pubmed.ncbi.nlm.nih.gov/37068504/	July 2023
2	Randomized 1:1, double-blinded, placebo-controlled, phase 3 trial	Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial.	GLOW (NCT03653507) Patients (≥18 years) with CLDN18.2 expression in ≥75% tumour cells and HER2-negative. N= 254, zolbetuximab (800 mg/m2 loading dose followed by 600 mg/m2 Q3W plus CAPOX + or N= 253, placebo IV Q3W plus CAPOX	https://www.nature.com/articles/s41591-023-02465-7	2023
3	Randomized, double-blinded, placebo-controlled, phase 2 trial	FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma.	FAST (NCT01630083) Patients (≥18 years) with CLDN18.2 expression in ≥40% tumour cells. Arm1, n= 84, first-line epirubicin + oxaliplatin + capecitabine (EOX Q3W); Arm 2, n= 77, zolbetuximab + EOX (loading dose, 800 mg/m^2 then 600 mg/m^2 Q3W) Arm 3 (exploratory), n=85, added after enrolment initiation (zolbetuximab + EOX 1000 mg/m^2 Q3W	https://pubmed.ncbi.nlm.nih.gov/33610734/	2021

References:

[i] Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2016;27(suppl 5):v38-v49.

[ii] Quante M, Wang TC, Bass AJ. Adenocarcinoma of the oesophagus: is it gastric cancer? *Gut.* 2023;72(6):1027-1029.

[iii] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021;71(3):209-249 .

[iv] [4] Quaresma M, Coleman MP, Rachet B. 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971-2011: a population-based study. *Lancet.* 2015;385(9974):1206-1218.

[v] Grizzi G, Venetis K, Denaro N, et al. Anti-Claudin Treatments in Gastroesophageal Adenocarcinoma: Mainstream and Upcoming Strategies. *J Clin Med.* 2023;12(8).

[vi] Hashimoto I, Oshima T. Claudins and Gastric Cancer: An Overview. *Cancers (Basel).* 2022;14(2).

[vii] Wang DW, Zhang WH, Danil G, Yang K, Hu JK. The role and mechanism of claudins in cancer. *Front Oncol.* 2022;12:1051497.

[viii] Sahin U, Tureci O, Manikhas G, et al. FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. *Ann Oncol.* 2021;32(5):609-619.

[ix] Sahin U, Koslowski M, Dhaene K, et al. Claudin-18 splice variant 2 is a pan-cancer target suitable for therapeutic antibody development. *Clin Cancer Res.* 2008;14(23):7624-7634.

[x] Pellino A, Brignola S, Riello E, et al. Association of CLDN18 Protein Expression with Clinicopathological Features and Prognosis in Advanced Gastric and Gastroesophageal Junction Adenocarcinomas. *J Pers Med.* 2021;11(11).

[xi] Bickenbach K, Strong VE. Comparisons of Gastric Cancer Treatments: East vs. West. *J Gastric Cancer.* 2012;12(2):55-62.

[xii] Jun KH, Kim JH, Jung JH, Choi HJ, Chin HM. Expression of claudin-7 and loss of claudin-18 correlate with poor prognosis in gastric cancer. *Int J Surg.* 2014;12(2):156-162.

[xiii] Sentani K, Oue N, Tashiro T, et al. Immunohistochemical staining of Reg IV and claudin-18 is useful in the diagnosis of gastrointestinal signet ring cell carcinoma. *Am J Surg Pathol.* 2008;32(8):1182-1189.